Phase II study of preoperative radiation plus concurrent daily tegafur-uracil (UFT) with leucovorin for locally advanced rectal cancer

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Résumé en anglais	BACKGROUND: Considerable variation in intravenous 5-fluorouracil (5-FU) metabolism can occur due to the wide range of dihydropyrimidine dehydrogenase (DPD) enzyme activity, which can affect both tolerability and efficacy. The oral fluoropyrimidine tegafur-uracil (UFT) is an effective, well-tolerated and convenient alternative to intravenous 5-FU. We undertook this study in patients with locally advanced rectal cancer to evaluate the efficacy and tolerability of UFT with leucovorin (LV) and preoperative radiotherapy and to evaluate the utility and limitations of multicenter staging using pre- and post-chemoradiotherapy ultrasound. We also performed a validated pretherapy assessment of DPD activity and assessed its potential influence on the tolerability of UFT treatment. METHODS: This phase II study assessed preoperative UFT with LV and radiotherapy in 85 patients with locally advanced T3 rectal cancer. Patients with potentially resectable tumors received UFT (300 mg/m/2/day), LV (75 mg/day), and pelvic radiotherapy (1.8 Gy/day, 45 Gy total) 5 days/week for 5 weeks then surgery 4-6 weeks later. The primary endpoints included tumor downstaging and the pathologic complete response (pCR) rate. RESULTS: Most adverse events were mild to moderate in nature. Preoperative grade 3/4 adverse events included diarrhea (n = 18, 21%) and nausea/vomiting (n = 5, 6%). Two patients heterozygous for dihydropyrimidine dehydrogenase gene (DPYD) experienced early grade 4 neutropenia (variant IVS14+1G > A) and diarrhea (variant 2846A > T). Pretreatment ultrasound TNM staging was compared with postchemoradiotherapy pathology TN staging and a significant shift towards earlier TNM stages was observed ($p < 0.001$). The overall downstaging rate was 42% for primary tumors and 44% for lymph nodes. The pCR rate was 8%. The sensitivity and specificity of ultrasound for staging was poor. Anal sphincter function was preserved in 55 patients (65%). Overall and recurrence-free survival at 3 years was 86.1% and 66.7%, respectively. Adjuvant chemotherapy was administered to 36 node-positive patients (mean duration 118 days). CONCLUSION: Preoperative chemoradiotherapy using UFT with LV plus radiotherapy was well tolerated and effective and represents a convenient alternative to 5-FU-based chemoradiotherapy for the treatment of resectable rectal cancer. Pretreatment detection of DPD deficiency should be performed to avoid severe adverse events.
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